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Interstitial Deletion 5p Accompanied by Dicentric Ring Formation of the Deleted Segment Resulting in Trisomy 5p13-cen

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Karyotypes with an interstitial deletion and a marker chromosome formed from the deleted segment are rare. We identified such a rearrangement in a newborn infant, who presented with macrocephaly, asymmetric square skull, minor facial anomalies, omphalocele, inguinal hernias, hypospadias, and club feet. The karyotype 46,XY,del(5)(pter→p13::cen→qter)/47,XY,+dicr(5)(:p13→cen::p13→cen), del(5)(pter→p13::cen→qter) was identified by banding studies and FISH analysis in the peripheral lymphocytes. One breakpoint on the del(5) maps distal to GDNF, and FISH analysis using an α-satellite probe suggests that the proximal breakpoint maps within the centromere. The dicentric r(5) consists of two copies of the segment deleted in the del(5), resulting in trisomy of proximal 5p (5p13-cen). The phenotype of the propositus is compared with other trisomy 5p cases and possible mechanisms for the generation of this unique chromosomal rearrangement are discussed.

KEY WORDS: chromosome 5, partial trisomy, centromere, dicentric ring chromosome

INTRODUCTION

Interstitial deletion accompanied by the formation of a marker chromosome that is formed from the deleted segment is a rare type of constitutional chromosomal abnormality. Such a rearrangement has been described for chromosome 9 [Pfeiffer et al., 1991; Smith et al., 1973], 10 [Turleau et al., 1979; Voullaire et al., 1993], 12 [Donlon et al., 1992], 16 [Krauss et al., 1987], and 17 [Andersen et al., 1990; Friedman et al., 1992]. Most carriers are phenotypically normal [Donlon et al., 1992; Friedman et al., 1992] or have only minor phenotypic abnormalities [Andersen et al., 1990; Krauss et al., 1987; Pfeiffer et al., 1991; Voullaire et al., 1993].

Here we describe an infant with a deletion of the short arm of chromosome 5 and an extra ring chromosome. Cytogenetic and fluorescence in situ hybridization (FISH) studies showed that the ring chromosome consists of two copies of segment 5p13-cen, which is missing in the del(5).

Comparison of the phenotype of the propositus and of other patients with trisomy 5p suggests that the trisomy 5p13-cen is correlated with the clinical signs observed in the propositus.

CLINICAL REPORT

The propositus BF is the first child of normal, nonconsanguineous parents. Mother was 25 and father 28 years old. Family history was unremarkable. BF was born at term by cesarean section after an uneventful pregnancy. He had a birth weight of 3,500 g (50th centile), a length of 50 cm (25th centile), and a head circumference (OFC) of 38 cm (>95th centile).

Physical examination demonstrated the following craniofacial manifestations (Fig. 1): a square asymmetric skull with plagioturricephaly and facial asymmetry, hypertelorism, epicanthal folds, short and broad nose with a broad and flat nasal bridge, long and deep philtrum, microretrognathism, high palate, and apparently low-set abnormally modelled ears. Clinodactyly V and simian crease were present on both hands. Muscular hypotonia, an omphalocele, inguinal hernias, and club feet were noted. There were no further organ defects. His voice was high, but differed from the cry of infants with cri du chat syndrome.

Routine laboratory findings were normal.

At the age of 20 months, he had a length of 85 cm (50th centile), weight of 14 kg (90th centile), and OFC

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Fig. 1. Patient BF at the age of 2 weeks.

of 52 cm (>97th centile). His psychomotor development was delayed. At 2.5 years, he was unable to walk without assistance, and he spoke only a few simple words.

Cytogenetics and FISH

Chromosomes were prepared from peripheral lymphocytes of the propositus and his parents. GTG- and CBG-banding were carried out according to standard procedures. Chromosomal analysis by GTG-banding in the propositus resulted in the following karyotype: 46,XY,del(5)(p13cen)[2]/47,XY,del(5)(p13cen),+r(?)[68]. The extra marker chromosome appeared as a small ring, with a size larger than the deleted segment of del(5). The centromeric region of del(5) showed a smaller centromeric constriction than the normal homologue in GTG-banding and a weaker C-band in CBG-staining (Fig. 2). These findings suggested that one breakpoint of the del(5) occurred within the centromeric region. The small ring chromosome contains two CBG-positive regions in all 30 analyzed metaphases. Normal karyotypes were found in the parents.

FISH using a biotinylated α-satellite probe (Oncor, Inc., Gaithersburg, MD) which hybridizes to the centromeric region of chromosomes 1, 5, and 19 (probes D1Z7/D5Z2/D19Z3) was performed according to the manufacturers instructions. One fluorescence signal was observed on the centromeric regions of each chromosome 1, 5, and 19 and two signals were seen on the ring chromosome (30 metaphases), confirming that the marker represents a dicentric ring chromosome. Again, the centromeric signal on del(5) was weaker than that of the normal homologue (Fig. 3). FISH analysis using a DNA library of chromosome 5 was carried out according to Lichter et al. [1988], and showed signals over the whole length of the dicentric ring, del(5), and the normal homologue (not shown). This provides further evidence that the small ring chromosome is of chromosome 5 origin. FISH, using the YAC clone 897G2 from the human CEPH "B" Mega-YAC library, which contains the GDNF gene and was recently mapped to 5p12-13, was performed as decribed elsewhere [Schindelhauer et al., 1995].

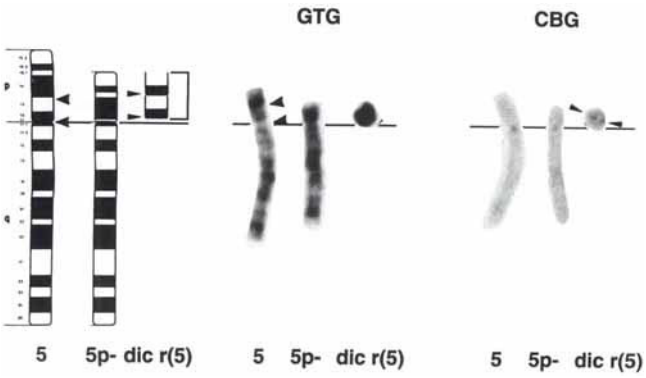

Fig. 2. Ideogram and partial karyograms of the propositus. Breakpoints are indicated by large arrowheads in GTG-staining. Note the weak C-band on the del(5) and the two C-bands on the r(5) (small arrowheads).

The expected signals on 5p12/13 of the normal chromosome 5, and a stronger signal or sometimes two distinct signals on the ring were observed, while no signal could be detected on del(5p) (20 metaphases). Hybridization signals were also found on chromosome 2p and are due to chimerism of the YAC [Schindelhauer et al., 1995] (not shown). Altogether, the marker chromosome can be designated as a dicentric ring chromosome r(5)(:p13→cen::p13→cen:) (Fig. 2).

DISCUSSION

GTG-, CBG-banding, and FISH studies demonstrated a unique chromosomal rearrangement in the propositus. He showed an interstitial deletion on the short arm of chromosome 5 and an extra dicentric ring chromosome consisting of two copies of the deleted segment 5p13-cen in most examined lymphocytes, which results

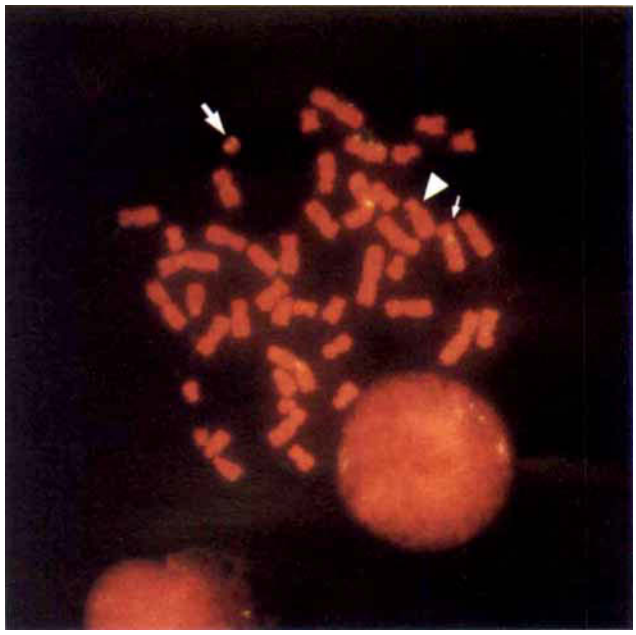

Fig. 3. FISH analysis of a metaphase of the propositus using an α-satellite probe of chromosomes 1, 5, and 19 (Oncor). A signal is present at the centromere of the normal chromosome 5 (small arrow). The del(5) shows a weaker signal (arrow head), and two signals are visible on the r(5) (large arrow). Further hybridization signals are present at the centromeres of chromosomes 1 (strong signal) and 19 (weak signal).

in partial trisomy 5p. A small percentage of cells showed pentasomy and monosomy 5p13-cen due to mosaicism with two dicentric r(5) and lack of the dicentric r(5), respectively. Mitotic instability resulting in somatic mosaicism is a well-known characteristic of ring chromosomes [Kosztolányi, 1987]. Therefore, mosaicism for the dicentric r(5) and even for a monocentric r(5) might also be present in other tissues. A submicroscopic deletion within the breakpoint areas cannot be excluded.

Partial trisomies of the short arm of chromosome 5 have been reported in more than 40 patients [Kleczkowska et al., 1987]. Most of these imbalances represent double segment aneuploidies, which result from parental reciprocal translocations or from parental inversions. Isolated trisomy for the whole p-arm of chromosome 5 has been described in patients with isochromosome 5p [Cordero et al., 1977; Fujita et al., 1994; Leschot and Lim, 1979; Orye et al., 1983; Stanley et al., 1993], and in patients with translocation of the whole 5p onto the p-arm of an acrocentric chromosome [Brimblecombe et al., 1977; Carnevale et al., 1982]. Isolated partial trisomy 5p has been reported in at least eight cases. The four patients with trisomy of the segment p14-p15 showed a mild phenotype with moderate mental retardation [Chen et al., 1995; Chia et al., 1987; Webb et al., 1988; Zenger-Hain et al., 1993], while those patients with trisomy of a larger segment including 5p13 [Gustavson et al., 1988; Kleczkowska et al., 1987; Leichtman et al., 1991; Rethoré et al., 1989] were more severely affected. We are not aware of a case with a trisomy 5p identical to that of our patient.

The phenotype of patients with partial trisomy of the proximal segment of 5p is different from the phenotype of patients with partial trisomy of distal 5p. Typical manifestations are macrocephaly, club feet, heart defect, tracheobronchial defects with subsequent respiratory infections, muscular hypotonia, psychomotoric delay, broad and depressed nasal bridge, microretrognathism, and abnormal ears [Fujita et al., 1994]. These traits are also present in our patient suggesting that the trisomy 5p13-cen is present in most cells and is responsible for his phenotype, consistent with the hypothesis that the trisomy 5p phenotype may be largely attributed to the segment 5p11-13 [Chia et al., 1987]. In our propositus and in a patient with a nonmosaic trisomy 5p12-p15.3 [Leichtman et al., 1991], the macrocephaly was accompanied by a square asymmetric skull and an asymmetric face, suggesting that gene(s) which play a role in craniosynostosis may be located in the duplicated area.

The generation of a marker chromosome with a functional centromere from an interstitial segment of a deleted stable chromosome can be explained by at least three different mechanisms. First, a break occurred within an intact centromere resulting in two active, but smaller centromeres. Second, centromeric sequences are duplicated before or during the rearrangement process. Third, a latent centromere gets reactivated which might be located in the vicinity of the active centromere or far away of it. Reactivation of a latent centromere on 10q was suggested in an unusual rearrangement of chromosome 10 by Voullaire et al. [1993]. In contrast, findings in a chromosome 17 rearrangement [(del(17q) + r(17)] favour the first mechanism [Andersen et al., 1990; Friedman et al., 1992; Wevrick et al., 1990; Willard et al., 1988]. The del(5) of our patient shows only a weak primary constriction in GTG-banding, a small heterochromatic C-band, and a weak fluorescence signal for alphoid DNA compared with its normal homologue, which suggests centromere splitting. Because both the del(5) and the dicentric r(5) contain alphoid sequences, the breakpoint should be within the α-satellite DNA sequences. The dicentric r(5) could arise in early postzygotic mitosis by sister chromatid exchange in a monocentric r(5), which is a common mechanism for the formation of dicentric ring chromosomes.

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